Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer

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Dylan M. Zylla, MD

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Faculty Advisor: Pankaj Gupta, MD

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Dedication

I would like to dedicate this thesis to my parents, Eugene and Joanne Zylla and Rich and Carol Bergenstal, who helped get me on the right path in both life and medicine; and my wife, Emily Zylla, who ensures I have the love and support I need every step along that path. And also to my research mentor and friend, Pankaj Gupta, who has given me the skills and confidence to forge my own road.

Abstract

Background: Pain is associated with shorter survival in non-small cell lung cancer (NSCLC). Lung cancer cells express opioid receptors. Opioids promote angiogenesis, tumor growth and metastases, and shorten survival in animal models.

Methods: To examine if long-term opioid requirement, independently of chronic pain, is associated with survival, we studied 209 patients treated with chemotherapy for stage IIIB/IV NSCLC. Pain was stratified by proportion of time patients reported specific levels of pain. Opioids were converted to oral morphine equivalents (OME) for comparison. The effects of pain, opioid requirement, and known prognostic variables on survival were analyzed in univariable and multivariable models.

Results: Both severity of pain and greater opioid requirement in first 90 days after starting chemotherapy were strongly predictive of shorter survival on univariable analysis. Patients with no/mild chronic pain and requiring <5 mg/day OME during first 90 days had nearly 12 months longer median survival compared to patients requiring ≥5 mg/day OME and/or experiencing more pain. Differences in survival remained remarkably similar when chronic pain and opioid requirement were assessed over the entire clinical course (until death or last follow-up). In multivariable models, both opioid requirement and chronic pain remained independent predictors of survival, after adjustment for age, stage and performance status.

Conclusions: Severity of chronic cancer-related pain or greater opioid requirement are associated with shorter survival in advanced NSCLC, independently of known prognostic factors. While pain adversely influences prognosis, controlling it with opioids does not improve survival. Prospective studies should determine if achieving pain control using opioid-sparing approaches improves outcomes.

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Introduction

Cancer related pain is common, negatively impacts quality of life, and often requires opioid analgesics. Two-thirds of patients with advanced malignancies experience pain, with almost 50% experiencing moderate-severe pain.[1] Opioid medications are the mainstay of treatment of severe, chronic cancer pain.[2, 3] Experimental studies and retrospective clinical analyses raise the concern that opioids might promote cancer progression and reduce survival.[4-18]

The role of the mu-opioid receptor

Morphine and other opioids are the mainstays of pain management in cancer patients.[2] Opioids exert their analgesic effects through opioid receptors. The mu-opioid receptor (MOP-R) is one of 4 major opioid receptors. MOP-R expression has been demonstrated in cancers of the breast, lung, prostate, colon, and esophagus.[4, 18-20] There is a complex interplay among cancer pain, exogenous opioids (eg, morphine), endogenous opioids (eg, beta-endorphins), MOP-R, and cancer growth and progression (**Figure i**).[21]

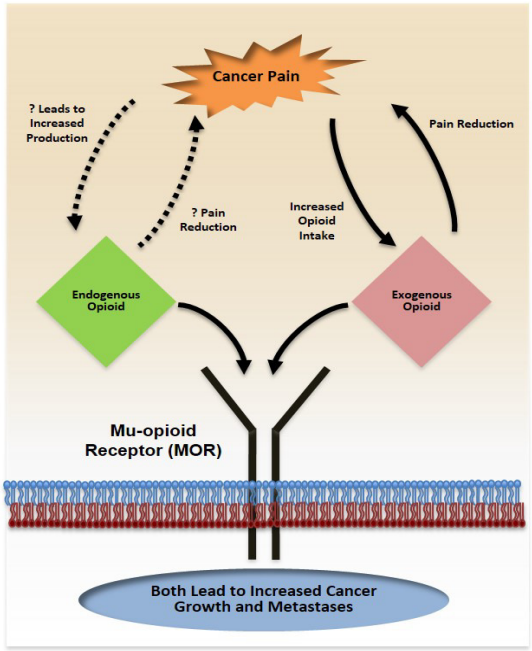

Figure i. Overview of cancer pain, opioids, the mu opioid receptor, and cancer progression

Clinical studies of opioids, cancer progression and the mu-opioid receptor

Clinical studies also suggest that MOP-R and opioid exposure are associated with inferior survival in patients with advanced malignancies.[18, 22-24] We have reported that the level of

MOP-R expression in samples from patients with prostate cancer was independently associated with worse OS.[18] Others have shown that blocking MOP-R with methylnaltrexone is associated with lower rates of tumor progression in patients with advanced cancers.[25] In addition, genetic polymorphisms in MOP-R have been associated with both increased breast cancer development and decreased breast cancer-specific survival.[22, 26]

In a retrospective study of patients with advanced prostate cancer receiving androgen deprivation therapy, we found that greater opioid requirement and higher levels of MOP-R expression in the tumor specimen are independently associated with shorter progression-free survival (PFS) and overall survival (OS).[18]

Because high MOP-R expression was associated with shorter OS, we conducted a subset analysis in prostate cancer patients with high MOP-R, stratified on opioid exposure (n=36 total patients, unpublished findings). Of patients with high MOP-R, those with LOE (n=13) had longer OS than those with HOE (n=23) (median OS, 503 vs. 387 days, *P*=0.05, **Figure ii.**).

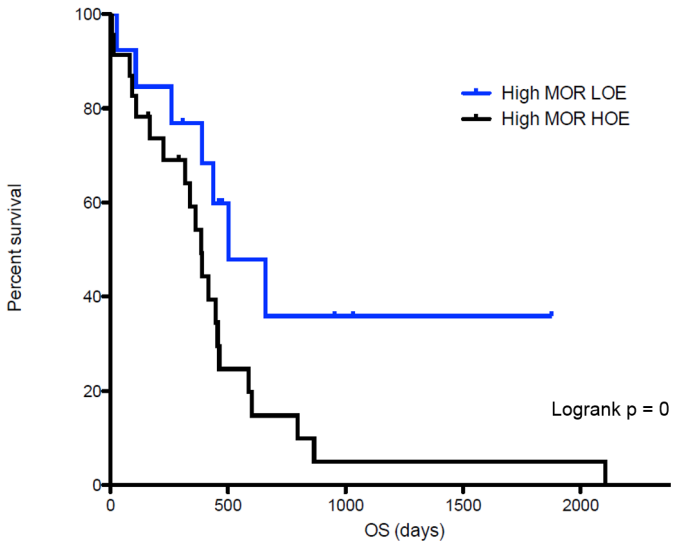

Figure ii. Kaplan-Meier curves for overall survival in patients with hormone-sensitive metastatic prostate cancer with high mu opioid receptor expression based on opioid exposure (N=36).

These data suggest that high baseline MOP-R levels alone may have a negative affect (because endogenous opioids alone may induce MOP-R's growth-promoting properties) and that patients using high amounts of exogenous opioids may have shorter OS due to excessive MOP-R activation. These data indicate that baseline MOP-R expression may strongly predict both response and long-term survival, independent of other key factors. This is consistent with laboratory and animal evidence suggesting an association of MOP-R expression, opioids, and cancer progression. These findings require confirmation in other tissue samples from patients with other advanced cancers. If results are consistent, it would warrant larger clinical trials to further assess the effect on treatment.

More recently, Halabi et al. confirmed and extended our findings to patients with advanced prostate cancer receiving first-line chemotherapy, reporting that opioid use is an independent prognostic factor for survival.[27] Some prospective studies suggest that systemic exposure to endogenous or pharmacological opioids may promote cancer progression in patients with astrocytomas,[28] pancreatic cancer[29] and various advanced solid tumors including lung cancer.[30].

The role of pain and opioids in lung cancer

Pain at diagnosis is itself associated with shorter survival in lung cancer[31, 32] and other malignancies.[27, 33-38] Pain may induce cancer progression via tumor innervation[39] and release of tachykinins such as substance P,[40] endogenous opioid peptides that modulate immune function,[41] or cyclo-oxygenase-mediated release of prostaglandins.[42, 43] Therefore, it is not clear whether reduced survival in patients treated with opioids is due to opioids and/or pain. Since pain has a direct impact on the quality of life and perhaps disease outcomes, it is critical to understand the independent contribution of pain and opioids to cancer progression and survival, to develop appropriate strategies to improve outcomes in patients with malignancies.

Lung cancer is the most common malignancy worldwide,[44] and ranks third highest for pain prevalence out of all malignancies.[1]. Pre-clinical data on cellular mechanisms and murine models demonstrate that opioids promote lung cancer progression and metastasis and reduce survival.[5, 6, 14, 16] Opioids via MOP-R directly activate mitogenic signaling and also by co-activating receptor tyrosine kinases (RTKs) including vascular endothelial growth factor receptor-2 (VEGFR2) and epidermal growth factor receptor (EGFR) in endothelial[4] and lung cancer cells.[5, 6, 14, 16] respectively, and epithelial-mesenchymal transition.[16] MOP-R expression is increased in several different human lung cancer tissues as compared to normal human lungs.[5, 45] These findings suggest the possibility that opioids may be associated with lung cancer progression in patients.

Rationale for current study

The above studies did not differentiate between the impact of pain and opioid use independently of the other. These previous studies also did not evaluate the effect of chronic (ongoing) pain or long-term quantitative opioid exposure on cancer outcomes. Furthermore, there is marked inter-patient variability in treatment of pain and use of opioids, depending upon individual patients' pain thresholds and patient and provider pain management preferences.[2, 3] Therefore, in this retrospective analysis, we objectively determined the effect of chronic cancer-related pain and quantitative systemic opioid use, independent of each other, on survival of patients with advanced NSCLC.

Methods

Patients

We analyzed data on 209 patients diagnosed with stage IIIB/IV non-small cell lung cancer from 2003-2010 at the Minneapolis Veterans Affairs (VA) Health Care System (MVAHCS) who were treated with palliative chemotherapy, to determine whether pain or opioid requirement is associated with survival. Demographic, clinical, and pharmacy data were obtained from patient records, the tumor registry, and VA Data Support Services. The study was approved by the institutional Human Subjects Committee.

Opioid Requirement

All oral and transdermal outpatient opioid prescriptions dispensed from any VA in the USA from 2002-2012 were collected to determine the total opioid quantity dispensed per prescription. All opioid prescriptions were converted to oral morphine equivalents (OME) using an equi-analgesic conversion table, as previously described.[18] Average daily opioid requirement was calculated for three distinct treatment intervals: 1) 90 days prior to chemotherapy initiation, 2) 90 days after chemotherapy initiation, and 3) chemotherapy initiation to death/last follow up.

Pain Levels

All pain values recorded from both inpatient and outpatient clinical encounters were collected on each patient. As with opioid requirement, pain levels were analyzed for each of the three treatment intervals (i.e., 90 days before chemotherapy, 90 days after starting chemotherapy, and from chemotherapy to death/last follow up). Severity of pain was categorized in accordance with the Brief Pain Inventory: low pain (pain levels 0-3), moderate pain (pain levels 4-6), and severe pain (pain levels 7-10).[46] For analysis of pain during the 90 days before chemotherapy, we used

the patient's maximum reported pain level (≥ 7 vs < 7) in order to maintain consistency and comparability with reported studies.

Pain-Opioid Groups

For treatment intervals after chemotherapy initiation, both pain and opioid requirement were separated into high and low groups to better assess for interactions (Table i.).

Table i. Categorization of pain levels and opioid requirement

	Low pain (LP) group	**High pain (HP) group**
Severe pain (level 7-10)	< 10% of all recordings	≥ 10% of all recordings
Moderate - severe pain (level 4-10)	< 25% of all recordings	≥ 25% of all recordings

	Low opioids (LO) group	**High opioids (HO) group**
Average oral morphine equivalents	< 5 mg/day	≥ 5 mg/day

Pain	*Opioid requirement: Low*	*High*
Low	**LPLO**	**LPHO**
High	**HPLO**	**HPHO**

Four subgroups were created based on pain levels and opioid requirements: (a) low pain/low opioid (LPLO: reference group against which the other 3 groups were compared), b) high pain/low opioid (HPLO), c) low pain/high opioid (LPHO), and d) high pain/high opioid (HPHO). For these groupings, pain was characterized as High (HP) or Low (LP) based on the definitions above. Analyses were performed separately using the severe pain or moderate-severe pain categorizations. Opioid requirement of ≥ 5 mg/day oral morphine equivalents (OME) was considered High (high opioid [HO]), and that < 5 mg/day OME as Low (low opioid [LO] group)

Pain was stratified by the proportion of time a patient reported severe pain (high pain [HP] group: ≥ 10% of all recordings, low pain [LP] group: < 10% of all recordings), or moderate-severe pain (HP group: ≥ 25% of all recordings, LP group: <25% of all recordings). Patients requiring ≥ 5 mg/day OME (the equivalent of the lowest single immediate-release tablet strength for morphine) were considered to have high use (thus, high opioid [HO] group: ≥ 5 mg/day OME, low opioid [LO] group: < 5 mg/day OME).

Four subgroups were created based on severity of pain and quantitative opioid requirement, reflecting the different clinical scenarios observed in clinical practice:[2, 3] (a) low pain/low opioid (LPLO), b) low pain/high opioid (LPHO), c) high pain/low opioid (HPLO), and d) high pain/high opioid (HPHO). The LPLO (reference) group included patients experiencing minimal pain and requiring no/minimal opioids. The LPHO group included patients with good pain control with high opioid utilization; the HPLO group comprised of patients experiencing higher levels of pain but no/minimal opioid utilization (perhaps due to patient preference or intolerability to opioids, or prescribing practices: a phenomenon well-recognized in the literature[2, 3]). The HPHO group included patients experiencing higher levels of pain despite higher opioid use. This grouping thus aimed to separate patients with chronic severe pain alone (HPLO) from those with higher opioid exposure alone (LPHO) from the reference group with neither of these factors (LPLO).

Statistical analysis

Cox proportional-hazards regression models were used to compare the subgroups for OS. The effects of individual factors on OS were evaluated using Kaplan-Meier analyses. For multivariable cox models, OS was analyzed after adjusting for known prognostic factors at time of diagnosis (age, performance status and stage of disease). Indicator variable coding was used to compare pain-opioid subgroups (LPLO, HPLO, LPHO, HPHO), with the LPLO serving as the reference group against which the other three groups were compared.

Results

Patient demographics

As shown in **Table ii**., the majority of patients were male (98%), had stage IV disease (71%), and had good performance status (75% had ECOG PS of 0-1). Nearly half had experienced severe pain (i.e., at least one pain level of 7 or higher) in the 90 days preceding chemotherapy, with a similar proportion receiving opioids prior to chemotherapy. These percentages show the population to be relatively high functioning with advanced disease, yet also balanced in regards to baseline pain and opioid requirement. The predominantly male VA population precludes generalization of our results to female patients.

Table ii. Baseline characteristics

		All patients (n=209)
Median age at diagnosis (range), years		63 (45-83)
Sex (male/female), %		98/2
Stage (IIIB/IV), %		29/71
Performance status (ECOG scale), %	0	20
	1	55
	2	22
	3	3
	4	0
Severe pain at diagnosis, %		46
Average opioid requirement at diagnosis (≥ 5 mg/day oral morphine equivalents), %		42

Association of pain level and opioid requirement with survival

We first examined in univariable models whether pain level or opioid requirement at different time periods during the course of the disease were associated with survival (**Table iii**.).

The presence of chronic severe pain, moderate-severe pain, or high opioid requirement in the first 90 days after initiation of chemotherapy, or during the entire treatment period (chemotherapy initiation to death/last follow up), was significantly associated with shorter OS. However, while patients experiencing a maximum pain level of 7 or higher prior to initiation of chemotherapy had shorter survival, greater opioid requirement prior to initiation of chemotherapy was not associated with survival.

Table iii. Association of chronic pain and opioid requirements with overall survival

Predictor interval	Predictor	Hazard ratio for overall survival (95% CI)	P-value
90 days prior to chemotherapy initiation	Maximum pain level (high vs low)[1]	1.39 (1.02 – 1.87)	0.035
	Opioid requirement (high vs low)[2]	0.92 (0.68 – 1.25)	0.606
First 90 days after chemotherapy initiation	Severe pain (high vs low)[3]	1.43 (1.02 – 2.00)	0.040
	Moderate-severe pain (high vs low)[4]	1.61 (1.17 – 2.21)	0.003
	Opioid requirement (high vs low)[2]	1.45 (1.07 – 1.96)	0.016
Chemotherapy initiation to last status date	Severe pain (high vs low)[3]	1.35 (0.99 – 1.86)	0.061
	Moderate-severe pain (high vs low)[4]	1.53 (1.11 – 2.11)	0.009
	Opioid requirement (high vs low)[2]	1.83 (1.32 – 2.55)	<0.001

[1]Maximum pain prior to chemotherapy: High-had at least one pain level ≥ 7 in the 90 days prior to chemotherapy initiation; Low-had all pain levels <7 in the 90 days prior to chemotherapy initiation.

[2]Opioid requirements during various time intervals: High: average opioid utilization of ≥5 mg/day oral morphine equivalents (OME) during time interval selected; Low: average opioid utilization of <5 mg/day OME during time interval selected.

[3]Severe pain during various time intervals: High: pain levels ≥ 7 on ≥ 10% of recordings during time interval selected; Low: pain levels ≥ 7 on <10% of recordings during time interval selected.

[4]Moderate-severe pain during various time intervals: High: pain levels ≥ 4 on ≥ 25% of recordings during time interval selected; Low: pain levels ≥ 4 on <25% of recordings during time interval selected.

Determination of the individual effects of pain level and opioid requirement on survival

We next attempted to differentiate the individual associations of pain and opioids with survival, using the pain/opioid groupings (LPLO [reference group], HPLO, LPHO and HPHO) described in the Methods. Analyses were performed for two time intervals in the clinical course (first 90 days after chemotherapy initiation, and chemotherapy initiation to death/last follow up) and for two pain stratifications (severe pain and moderate-severe pain). The probabilities of survival in each of these groups were estimated using Kaplan-Meier analyses (**Fig. iii**).

Association of pain and opioid requirement in the first 90 days after chemotherapy initiation with survival

Survival of patients in the LPLO (reference) group was significantly longer compared to the HPLO, LPHO, and HPHO groups (median survival,17.9 months vs. 5.7, 6.5, and 6.1 months, respectively, log-rank p value=0.002) stratified on the presence of severe pain (**Fig. iiiA**). Similarly, markedly different survivals were observed between the LPLO group and the other 3 groups when patients were stratified on the presence of moderate-severe pain (17.9 months vs. 5.7, 7.7, and 4.2 months, respectively, log-rank p-value=0.001; **Fig. iiiB**). These findings suggest that higher levels of pain and/or greater opioid requirement early in the treatment period are predictive of shorter survival in patients with advanced NSCLC.

Association of pain and opioid requirement during the entire clinical course with survival

Remarkably similar differences in survival were observed between the reference LPLO group and the other 3 groups when pain level and opioid requirement were assessed from chemotherapy initiation to death/last follow up. Median survival in the LPLO group was significantly longer compared to the HPLO, LPHO, and HPHO groups (16.0 months vs. 5.5, 6.5, and 7.8 months, respectively, log-rank p-value<0.001), stratified by severe pain (**Fig. iiiC**). Again, similar survival differences were seen using the moderate-severe pain stratification for this treatment interval

(16.4 months vs. 6.4, 7.1, and 7.7 months, respectively, log-rank p-value=<0.001) (**Fig. iiiD**). These findings indicate that the presence of chronic pain or high opioid requirement are associated with markedly shorter survival in patients with advanced NSCLC. Patients experiencing little to no pain and also consuming less than 5 mg oral morphine/day have considerably longer survival.

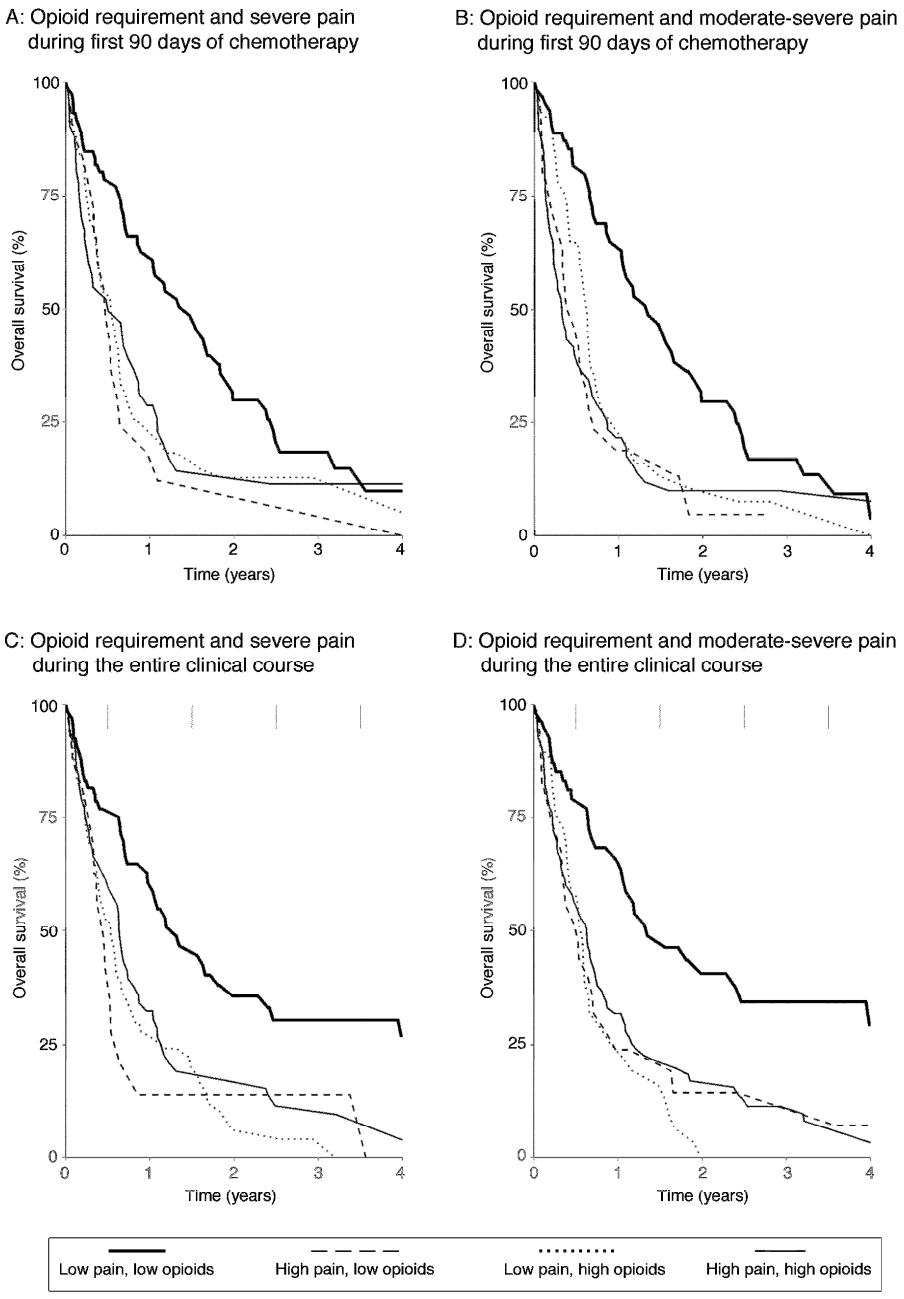

Figure iii. Overall survival based on pain and opioid requirement

Figure legend. The overall survival of patients experiencing different levels of chronic pain and requiring varying amounts of opioids (defined as described in the Methods and Table i) was estimated using the Kaplan-Meier method. The presence of higher levels of pain, greater opioid requirement, or both, was strongly associated with shorter survival. Significance of differences between the groups are provided in the Results section.

Multivariable analyses of pain, opioids and known prognostic factors

Finally, we evaluated if chronic pain level and/or opioid requirement are associated with differences in survival when clinical prognostic variables (age, performance status and stage of disease) are included in multivariable Cox regression analyses (**Table iv**.).

Table iv. Independent associations of chronic pain and opioid requirements with overall survival in multivariable models including known prognostic factors

	First 90 days after chemotherapy initiation				Chemotherapy initiation to last status date			
	Severe pain[1]		Moderate-severe pain[2]		Severe pain[1]		Moderate-severe pain[2]	
Predictor	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
HPLO[3]	2.62 (1.45-4.73)	0.001	2.11 (1.24 – 3.61)	0.006	3.21 (1.69 – 6.09)	<0.001	2.82 (1.61 – 4.96)	<0.001
LPHO[3]	1.91 (1.28 – 2.85)	0.002	1.80 (1.17 – 2.79)	0.008	2.07 (1.34 – 3.20)	0.001	2.15 (1.25 – 3.71)	0.006
HPHO[3]	2.01 (1.26 – 3.21)	0.003	2.12 (1.37 – 3.29)	0.001	2.28 (1.45 – 3.58)	<0.001	2.66 (1.69 – 4.21)	<0.001
Age	1.03 (1.01 – 1.05)	0.002	1.03 (1.01 – 1.04)	0.005	1.03 (1.01 – 1.05)	0.001	1.04 (1.02 – 1.06)	<0.001
Performance status (ECOG)	1.28 (1.04-1.58)	0.022	1.28 (1.03 – 1.59)	0.026	1.28 (1.05 – 1.58)	0.017	1.28 (1.03 – 1.58)	0.025
Stage (IIIB vs IV)	1.52 (1.25 - 1.86)	<0.001	1.52 (1.25 – 1.86)	<0.001	1.46 (1.19 – 1.78)	<0.001	1.46 (1.20 – 1.78)	<0.001

[1]Severe pain: High pain (HP)-had pain levels ≥ 7 on ≥ 10% of recordings during time interval selected; Low pain (LP)-had pain levels ≥ 7 on <10% of recordings during time interval selected.
[2]Moderate-severe pain: High pain (HP)-had pain levels ≥ 4 on ≥ 25% of recordings during time interval selected; Low pain (LP)-had pain levels ≥ 4 on <25% of recordings during time interval selected.
[3]Four subgroups were created based on pain levels and opioid requirements, as detailed in Table 1: (a) low pain/low opioid (LPLO: reference group against which the other 3 groups were compared; hazard ratio = 1.00), b) high pain/low opioid (HPLO), c) low pain/high opioid (LPHO), and d) high pain/high opioid (HPHO).

Longer survival of patients in the LPLO reference group remained significant for both pain classifications (severe pain or moderate-severe pain) and both treatment intervals (first 90 days after chemotherapy initiation or chemotherapy initiation to death/last follow up). In all these analyses, age, performance status and stage also remained significantly associated with survival, confirming the validity of the data set and outcomes. Of particular relevance, these results

indicate that chronic pain and/or higher opioid requirement in the first 3 months of treatment are individually and independently predictive of shorter survival in patients with advanced NSCLC.

Discussion

Quality of life and survival are influenced by pain and its treatment in cancer patients. However, it is not known if pain and analgesics influence these outcomes independent of one another or if their effect is inter-dependent. We show here for the first time that the presence of either chronic severe pain or greater quantitative opioid requirement is associated with markedly shorter survival in patients with advanced NSCLC, independent of known clinical prognostic factors.

The independent impact of chronic pain on clinical outcomes can be difficult to discern because it is often incorporated into different quality of life (QOL) assessment instruments that generate global QOL scores. To specifically examine the influence of chronic pain by itself on survival, we took advantage of the VA's electronic databases that document every pain level reported by inpatients and outpatients over the entire course of their disease; these databases provide a comprehensive assessment since patients in the VA system are rarely lost to follow up or go elsewhere for treatment. To minimize the disproportionate impact of single pain levels (which can fluctuate widely), we categorized patients with respect to the severity of chronic pain by calculating the proportion of times a patient reported pain above certain levels on a 0-10 scale over a longer period of time. This approach also allowed us to incorporate into our analyses all pain levels from any clinical encounter a patient had in the VA system.

Prior reports have separately shown that pain and opioid requirement are prognostic factors for OS in various malignancies,[18, 27, 31] but none of these studies simultaneously examined the individual or combined effects of both these inter-related factors. Segregating the severity of pain from opioid utilization poses a major challenge in such analyses. We were able to identify subgroups of patients experiencing higher levels of pain but not exposed to much opioids (the HPLO group), those experiencing little or no chronic pain but exposed to larger quantities of

opioids (the LPHO group), and those experiencing greater pain *and* exposed to higher amounts of opioids (HPHO group).[2, 3] Comparing these groups with a reference group of patients without much pain or opioid exposure (the LPLO group) allowed exploration of the potential impact of pain alone (HPLO group), opioids alone (LPHO group) or both factors on clinical outcomes. This strategy was able to identify highly significant and independent associations of pain and opioid requirement on overall survival, and may provide a useful method to evaluate the influence of these inter-related factors in other malignancies.

These clinical data complement earlier studies from our laboratory showing that chronic opioid administration leads to increased cancer progression and metastasis and reduced survival in mice with breast cancer.[7, 17] Hyperalgesia continued to increase in both control and morphine treated mice over time, but co-treatment with morphine and celecoxib (a COX-2 inhibitor) reduced hyperalgesia as well as cancer progression and metastasis and survival in these mice, suggesting that pain is associated with cancer progression and survival.[7] Opioid-induced hyperalgesia (OIH) may amplify existing pain, and may be an additional factor contributing to inferior outcomes in cancer. Thus, the present clinical observations together with earlier murine cancer studies demonstrate that pain may critically influence survival, independent of opioid use.

Recent studies in humans support the hypothesis generated by pre-clinical studies that stimulation of opioid receptor signaling promotes cancer progression, which in turn may also influence survival. Madar et al. showed using positron emission tomography that human lung cancers express higher levels of mu opioid receptors in vivo compared to adjacent normal lung tissue; binding of ligands (and thus likely also opioid medications and endogenous opioids) was effectively blocked by opioid antagonists in the tumor tissue in vivo.[45] These findings suggest that it may be possible to block the potential adverse effects of opioid receptor signaling in cancers. The need to examine the possible benefit of such strategies is underscored by our

observation in men with metastatic prostate cancer that both increased MOP-R expression and greater opioid requirement are independently associated with shorter progression-free and overall survival.[18]

Pain at diagnosis of lung cancer has been cited as a prognostic factor in patients with metastatic NSCLC. In a comprehensive literature search of pain in patients with stage IIIB/IV NSCLC, we found that pain at diagnosis was significantly associated with shorter survival on univariable analyses in approximately 80% of studies (unpublished results). Pain remained significant when clinical variables including age, gender, performance status, and stage of disease were included in multivariable analyses in some studies.[31, 32] However, none of these studies assessed the impact of chronic (long-term) pain, opioid requirement or MOP-R expression on outcomes. Consistent with these previous reports, we observed that the level of pain at diagnosis was significantly associated with survival. However, given the subjective and highly variable nature of pain, determination of a single pain level at diagnosis cannot reliably reflect the intensity (or influence) of chronic pain experienced by patients with advanced malignancies.

The poor survival of patients in the LPLO group may be related to the adverse effects of opioids. Alternatively, it is possible that pathways activated by pain[39-43] continue to exert their detrimental effects in advanced malignancies even after the perception of pain is relieved by opioid analgesics. Further investigation is required to distinguish between these possibilities.

Of note, the current study analyzed the association of chronic pain (from diagnosis till death) and quantitative, long-term opioid requirement with survival in patients with advanced cancer. Several retrospective[47-51] and one prospective[52] studies have examined the association of recurrence/survival with anesthetic technique and/or short-term peri-operative opioid administration in patients operated for early stage malignancies. However, the pharmacological

effects of opioids, immune function, opioid receptor expression and activity are likely quite different in the two settings.

Measuring the predictors (pain level and opioid requirement) concurrently with the outcome (survival) up till the time of death can introduce statistical bias. We therefore also analyzed the association of the predictors (pain and opioids) restricted to the first 90 days of chemotherapy (during which few patients died), with subsequent survival. Restricting analysis to the first 90 days after chemotherapy initiation also helped reduce the disproportionate impact of increasing pain and opioid requirement as patients approached the end of life (i.e., hospice care). In addition to avoiding statistical bias, our findings with this approach indicate that the severity of pain and quantitative opioid requirement early in the clinical course of advanced NSCLC are strongly and independently predictive of survival. Demonstrating significant and remarkably comparable associations with both pain predictors (severe pain or moderate-severe pain) and both analysis intervals (from initiation of chemotherapy to day 90, or from initiation of chemotherapy to death/last follow-up), further strengthens the validity of our findings.

The limitations of this study are that 1) it is retrospective, 2) opioid prescriptions dispensed were used as a measure of actual opioid consumption, 3) the confounding effect of tumor location and extent on pain levels, opioid requirements and outcomes could not be entirely excluded, and 4) it included the various histologies that are grouped under non-small cell lung cancer.

In conclusion, we report that patients with advanced non-small cell lung cancer experiencing more severe chronic cancer-related pain or having greater long-term opioid requirement are more likely to experience shorter survival, independently of the influence of known prognostic factors. Importantly, while pain is an independent prognostic factor, controlling it with opioid medications does not improve outcomes. Prospective investigations are warranted to determine if

managing pain with opioid-sparing approaches improves survival in patients with advanced malignancies. Until results of such studies are available, clinical practice aimed at relieving cancer pain should not be changed.

Future Directions

There is an urgent need for clinical translation of the in vitro, animal, and retrospective clinical data that suggest a negative effect of opioids on overall cancer survival. Given the high prevalence of cancer pain and corresponding use of opioids, any notion of opioids being "bad" may have dramatic repercussions for patients, providers, and policy-makers. While much is written about the management of cancer pain, few studies address how control of pain may affect clinical outcomes. MOP-R has an important role in cancer progression that is well defined with in vitro and in vivo studies, yet few have studied MOP-R expression, pain, and opioid use in patients with cancer. As such, I have expanded on the work in this thesis project with a number of research projects to help answer these important questions. These projects are summarized briefly below.

Impact of opioid use on health care utilization and survival in patients with newly diagnosed stage IV malignancies

Patients with advanced cancers frequently experience pain. Opioids are commonly prescribed to treat cancer-related pain, but their use might be associated with undesirable consequences including adverse effects and tumor progression, which may result in increased heath care utilization and shorter survival. We examined this possibility in a large cohort of patients diagnosed with ten common types of advanced malignancies.

We identified 1,386 patients with newly diagnosed stage IV non-hematologic malignancies from 2005-2013 and ascertained opioid utilization within 90 days of starting anti-cancer treatment using data from electronic health medical records and our tumor registry. Opioid utilization was stratified into low opioid (LO; < 5mg oral morphine equivalents (OME)/day) and high opioid (HO; ≥5 mg OME/day). Health care utilization included tallies of all emergency room, urgent

care, and inpatient visits. The association of opioid use, prognosis of tumor type, age, and gender with overall survival was analyzed in univariate and multivariate models.

HO use patients (n=624) had greater health care utilization at 3, 6, and 12 months after diagnosis compared to LO use patients (n=762; $p < 0.05$). HO use patients also had shorter survival compared to LO use patients (median survival, 5.5 vs 12.4 months; $p < 0.0001$). On multivariate analysis, HO use remained associated with shorter overall survival (HR 1.4; 95% CI, 1.3- 1.6; $p<0.0001$) after adjusting for age, gender and prognostic group (cancer type).

In patients with advanced cancer, HO use is associated with greater health care utilization and shorter survival. Prospective studies using opioid-sparing approaches are indicated, to confirm these retrospective findings and to evaluate if these undesirable effects associated with opioid use can be mitigated.

Mu-opioid receptor levels, opioid exposure, and survival in patients with stage IV pancreatic cancer

The purpose of this project is to: 1) measure MOP-R levels in human pancreatic cancer cells from a stored diagnostic biopsy sample; 2) determine the association between the level of MOP-R and OS of patients with pancreatic cancer; and 3) determine the joint relationship between MOP-R levels and opioid exposure on OS in this cohort.

Figure iii., the conceptual model for our proposal, is based on our OS estimates from the literature and our experience. We believe that those with high MOP-R expression and HOE will have inferior survival, especially compared with those with low MOP-R expression and LOE. Our proposal will allow determination of MOP-R expression of stored biopsies from patients with stage IV pancreatic cancer for whom mortality and opioid exposure data is available in the EHR. The goal is to determine if MOP-R expression and opioid exposure affected the OS. Tumor cell blocks from original biopsies will be used to address the relevance of this biological marker in determining best practices for pain management and OS in pancreatic cancer patients.

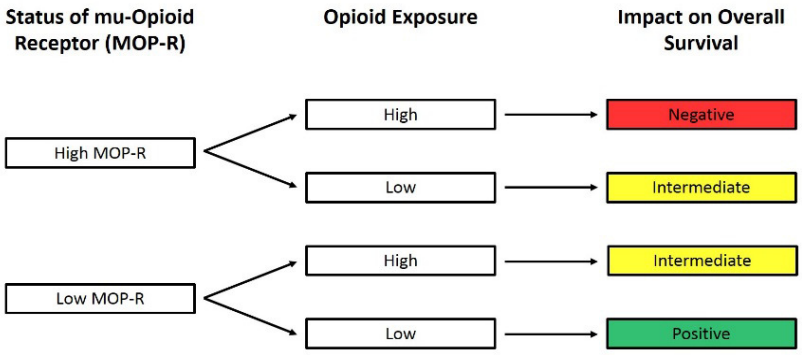

Figure iv. Conceptual model for MOP-R effects.

This is a retrospective study to quantify MOP-R levels in stored biopsies from deceased pancreatic cancer patients who presented with stage IV pancreatic cancer from 2005 to 2015 to the Health Partners Park Nicollet Frauenshuh Cancer Center, Minneapolis, MN. Data sources include stored biopsy tissue samples that will be analyzed for MOP-R expression and the EHR data warehouse for demographic, clinical, opioid exposure, and mortality data.

Using the EHRs at Frauenshuh Cancer Center, we have identified 90 deceased patients with stage IV pancreatic cancer diagnosed from 2005 to 2015. To be eligible for inclusion, patients needed pathology reports indicating a core needle biopsy of >0.5 cm in total length (fine needle aspiration or cytology were excluded because MOP-R analysis cannot accurately be ascertained

on these specimens) and needed adequate opioid use data during the first 90 days after chemotherapy initiation. The study pathologist will review the 90 diagnostic pathology reports from the pancreatic cancer patients identified for this project. The pathologist will locate and examine the paraffin blocks and slides of diagnostic tumor tissue obtained from core biopsies of metastatic sites to be used for the MOP-R testing to ensure that blocks have adequate tumor cells for analysis. From these 90 patients, we estimate that we will have at least 60 viable samples.

A Phase II Trial of Naloxegol in Metastatic Pancreatic Cancer Patients

We have submitted a proposal to conduct a prospective, single-arm study to assess the effects of a 16-week treatment with naloxegol in patients with metastatic pancreatic cancer. Naloxegol is a peripherally-selective opioid antagonist for the treatment of opioid-induced constipation. It was approved in 2014 in adult patients with chronic, non-cancer pain. Doses of 25 mg were found safe and well tolerated for 52 weeks. When given concomitantly with opioid analgesics, naloxegol reduced constipation-related side effects, while maintaining comparable levels of analgesia. We posit that early, ongoing use of naloxegol in patients with metastatic pancreatic cancer will not only provide optimal management of patient side effects (e.g., constipation) related to peripheral activation of mu receptor by opioids, but also will decrease angiogenic stimulus in tumor tissue, thereby reducing rate of tumor growth and metastases.

Patients with newly diagnosed (de-novo or recurrent) metastatic pancreatic ductal adenocarcinoma (PDAC) will be invited to join this study prior to initiation of standard therapy with gemcitabine and nab-paclitaxel [53]. Patients will be treated with 16 weeks of naloxegol along with gemcitabine and nab-paclitaxel and stratified by high or low mu-opioid receptor status. The primary endpoint will be assessment of Ca 19-9 levels.

A Randomized Trial of Medical Cannabis in Patients with Newly Diagnosed, Stage IV Lung and Pancreatic Cancers to Assess Impact on Cancer-Related Symptoms: A Pilot and Feasibility Study

Medical cannabis has been available in the state of Minnesota since July 2015, and has the potential to improve cancer related pain, chemotherapy-induced nausea and vomiting, along with other symptoms. In the first 15 months of the program, only 492 patients throughout the state of Minnesota received medical cannabis for cancer related symptoms. The overall safety profile of medical cannabis is still being explored, but serious adverse events in the Minnesota program appear rare. However, three factors severely limit use of medical cannabis in the cancer population; 1) the lack of rigorous scientific data demonstrating improvement in symptoms compared to usual care, 2) concerns from patients and clinicians on side effects, impact on current oncology treatments, and potential legal ramifications, and 3) a monthly cost to patients of approximately $300.

I am leading a workgroup with our Park Nicollet/HealthPartners research team, the Minnesota Department of Health, and leadership from both registered medical cannabis manufacturers in the state; LeafLine Labs and Minnesota Medical Solutions. The goal of our workgroup is to spearhead innovative research studies with medical cannabis as a focus. We have drafted a protocol for a randomized, observational study of medical cannabis use in patients with stage IV lung and pancreatic cancers to collect pilot data and support an NIH grant for a larger state-wide clinical trial through the Metro-Minnesota Community Oncology Research Consortium (MMCORC). We are seeking funding for this pilot study at Park Nicollet Frauenshuh Cancer Center (FRCC) and HealthPartners Regions Cancer Center (RCC) to determine feasibility and provide important pilot data for larger grant funding.

In collaboration with LeafLine Labs, Minnesota Medical Solutions, and the Minnesota Department of Health and the Office of Medical Cannabis, we will conduct a randomized clinical

trial to assess how early implementation of medical cannabis impacts cancer-pain, symptom management, and opioid utilization. The feasibility of recruiting/enrolling patients across institutions, conducting the study per protocol, and achieving good long-term follow-up will be a key aim in order to show this study can be expanded through MMCORC. Oncology patients with newly diagnosed, stage 4, lung and pancreas cancers meeting criteria for certification in the Minnesota's Medical Cannabis Program for the severe/chronic pain indication will be offered participation in study. Patients will be randomized 1:1 to early cannabis (EC) (n=25) vs delayed cannabis (DC) (n=25). The EC group will be provided with 3 months of medical cannabis at no charge. The DC group will receive usual care for the first 3 months, and then be provided 3 months of medical cannabis at no charge after 3 months. All patients will be required to complete a validated quality of life instrument (Patient-Reported Symptom Monitoring (PRSM)) every 28 days while in the study. The PRSM is a 23 question tool for oncology patients that addresses common symptoms (e.g., pain, nausea, fatigue, and depression), patient-assessed performance status, and overall quality of life.

Implementation of Electronic Patient-Reported Symptoms in Cancer Patients

We received grant funding to conduct a pilot project to build, test and evaluate uptake of an electronic Patient Reported Outcomes (ePROs) system to collect and track symptoms for oncology patients. Public and private investment and widespread adoption of the electronic health record (EHR) affords us the opportunity to incorporate the patient's voice and perspective on their symptoms directly into the EHR using the patient portal, MyChart. This project is applicable across our entire HealthPartners organization and nationally in other health care delivery systems. It will inform and extend our capacity for building electronic patient- reported outcomes, which is an organizational priority. The proposed system will deliver a validated symptom survey consisting of 23 questions and an internally generated pilot form consisting of 7

questions regarding the patient's individual pain goal and pain medication use. Both surveys will be delivered to consented study participants using EPIC MyChart. These data will then be directly integrated into our current EHR and will 1) generate symptom summary sheets that are available at point of care to patients and physicians and 2) be incorporated into a symptom flowsheet (discreet data points on each symptom) that will allow longitudinal follow up on each reported symptom. Successful completion of this pilot will allow us to extend the ePRO system to more of our oncology patient population as part of our standard of care and serve as a model for other HP departments. This system will allow patients, clinicians and researchers to capture, describe and manage complex symptoms and more fully incorporate the patient experience in symptom-generated clinical care protocols.

Patients with metastatic cancer have a high symptom burden. Symptom control measures, especially for pain, are highly correlated with overall patient satisfaction and survival. However, studies show clinicians often underestimate the symptom burden of their patients. One reason for this is that clinicians meet with patients at the start of chemotherapy cycles when symptoms from the previous treatment cycle have often improved. Yet, patient-reported symptoms, when efficiently collected and integrated into the EHR, can help care providers and patients make clinical decisions that have a positive impact on patient well-being.

Objective: To demonstrate the feasibility of building and implementing an ePRO system that will capture and extract patient-reported outcomes electronically using the integrated patient portal of our EHR (MyChart) for patients with stage IV cancer.

Specific Aims:

(1) To develop, test and evaluate an electronic data capture system that will collect electronic patient- reported outcomes(ePROS) using MyChart, the patient portal function of our EHR (EPIC)

(2) To build and extract a summary report of the ePRO from EPIC that is available at point of care to patients and providers

(3) To incorporate ePROs responses directly into EPIC flowsheet with discreet data fields that provides longitudinal data

In order to accomplish these aims, patients with stage IV non-hematologic cancers will be invited to consent to join this pilot study. We will develop and implement an ePRO system using the EPIC MyChart survey platform to administer the Patient-Reported Symptom Monitoring (PRSM) tool (University of North Carolina). The PRSM is a validated 23 question ePRO tool for oncology patients that addresses common symptoms (e.g., pain, nausea, fatigue, and depression), patient-assessed performance status, and overall quality of life. We will also continue to pilot an internally developed questionnaire regarding the individual Personalized Pain Goal and Medication Use (PGMU). Patients will complete the surveys every 14 days (+/- 2 days) via MyChart online.

Alternative methods of survey completion will be available, if necessary, via telephone completion or during clinic visits. Upon completion, data will be stored in a flow sheet format within Epic and a PRSM summary report will be generated for use at the next patient/provider visit. This electronic system will be developed and piloted during the first 5 months of the grant period and data collection will commence at month 6. Data collection will continue for 5 months, followed by data analysis and dissemination.

Successful completion of this study will demonstrate the feasibility of utilizing an ePRO system that is directly linked to EPIC. We will leverage the results of this study to submit a National Institutes of Health (NIH) or Patient-Centered Outcomes Research Institute (PCORI) grant proposal to more fully test and evaluate this system in our Cancer Centers. We hope to then extend this ePRO system to obtain funding to develop a clinical decision support (CDS) tool to assure patients receive the best practices available to alleviate their symptom burden.

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